Acta Biomed 2014; Vol. 85, N. 3: 189-204

Review

Therapeutic approach to "diabetic foot" complications

Cristina Calderini, Federico Cioni, Silvia Haddoub, Francesco Maccanelli, Maria Grazia Magotti, Sergio Tardio

SSD (Scientific-Disciplinary Area) Intensive treatment of diabetes and its complications, University Hospital of Parma, Parma, Italy

Summary. The series of ulcers of the lower extremities known as "diabetic foot" is a common complication of diabetes and the chief cause of admission to hospital. The causes may be numerous but the main ones are distal symmetric neuropathy and peripheral obliterative arteriopathy, often complicated by infection. In this review, the Authors, after having illustrated the main pathophysiological aspects of the diabetic foot, describe the clinical characteristics of the disease, focusing particularly on the risk of suprainfection and vascular problems. The clinical and therapeutic approach to diabetic foot is also investigated with particular reference to the antibiotic treatment of infections and the treatment of peripheral arterial disease. Poor tissue repair, persistent inflammation, the presence of deep abscesses, osteomyelitis and systemic involvement can lead to a very serious clinical picture of gangrene or necrosis, which is initially localised but which can extend widely, requiring minor or major amputation surgery, in order to radically remove the infected tissue. In conclusion, space for discussion is given to the rationale of hyperbaric oxygen therapy, negative pressure wound therapy and other advanced therapies that involve the use of dermoepidermal equivalents and skin substitutes in addition to gels made of platelet-derived growth factors and the epidermal growth factor. Nonetheless, prevention is, of course, of fundamental importance, based on an intensive treat-to-target approach for the treatment of diabetes, on regular examinations of the feet, on the stratification of risk and education of the patient, which has proved successful in reducing the onset of foot lesions in at least 50% of patients. (www.actabiomedica.it)

Key words: diabetes mellitus, diabetic foot, diabetic ulcer, charcot foot, wound healing

Preliminary remarks

In the natural history of diabetes mellitus, ulcers of the lower extremities are very common (1) and are defined as "diabetic foot". This disease has a multitude of causes, but the main aetiologies consist of two chronic complications of the disease: distal symmetric neuropathy and peripheral obliterative arteriopathy (2) often accompanied by infection.

"Diabetic foot" is the main cause of hospitalisation in diabetic patients (3) due to infection, gangrene, amputation surgery and the correction of Charcot foot. Over 60% of non-traumatic thigh or knee amputations are performed on diabetic patients (4-6), and the risk of amputation, which increases from 15 to 40 times in studies on these populations (7, 8), is parallel to the prevalence of both neuropathy and of vasculopathy (9).

In actual fact, a combination of many factors can slow down the healing process of a foot ulcer: ischaemia, infection, wound management, discharge and the presence of comorbidities (10).

Over recent years, some studies have reported a decrease in the incidence of major amputations (11, 12) probably due to the multidisciplinary approach to the disease, which involves various categories of professional figures, and thanks to the launching of prevention programmes which identify subjects at risk with a view to including them in an education programme in order to be able to monitor them effectively and implement suitable therapeutic actions.

The pathophysiology of the diabetic foot

The pathophysiological moments that contribute to the genesis of the alteration of the anatomo-functional alterations of the diabetic foot derive from the sum of autonomic sensory-motor neuropathy and peripheral vascular disease (2). Depending on the presence of one or other of these aspects, we can have neuropathic foot, ischaemic foot or, more frequently, neuro-ischaemic foot, given the simultaneous presence of neuropathy and vasculopathy (Diabetic Foot Disorders).

Diabetic neuropathy

Diabetic neuropathy involves sensory, somatic and autonomic fibres indiscriminately, causing specific alterations that transform into clinical manifestations of neuropathic foot.

In addition to generating the typical stocking-glove dysesthesias, impairment of the sensory pathways also makes the foot insensitive to the tactile and pain stimuli responsible for the mechanisms that defend it from external noxae, be they physical or chemical in nature. The patient also loses the capacity to feel and therefore, is unable to correct the plantar overload areas responsible for the formation of calluses, which then lead to neuropathic ulcers. These, in fact, often present as a plantar ulcer with a typical hyperkeratotic border, a signal of chronic plantar overload (13, 14). Damage to the motor component is followed by trophic changes in the muscles of the innervated districts, which generate a series of anatomical alterations in the foot. Hypotonia is observed followed by hypotrophy of the intrinsic muscles causing an imbalance of the action between the flexor and extensor muscles, which leads to a deformation in the architecture of the foot. Frequently, the muscles of the anterior loggia of the leg are affected with the onset of equinus, hammer toes, pes cavus and protrusion of the metatarsal heads. Moreover, the glycation of tendon and capsular collagen makes these structures hypoelastic, limiting the degree of freedom of the joints and contributing to the generation of plantar overload.

Impairment of the autonomic nervous pathways brings about a reduction in the physiological tonic control of the sympathetic nervous system at a microcirculatory level, and of the sweat glands of the foot. Therefore, an increase in the pedal blood flow is observed with the opening of arteriovenous shunts, which make the foot hot, swollen and with turgid dorsal veins due to increased venous return. Decreased sweating causes progressive xeroderma, which leads to the skin having poor elasticity, being flaky and prone to cracking. These lesions are particularly prone to the risk of infection inasmuch as the alterations in the skin pH secondary to anhidrosis favour the development of a microbial flora likely to harbour more potential pathogens. The most serious expression of the neuropathic foot is clinically manifested in Charcot's arthropathy, which is also known as "Charcot foot". In this case, the serious anatomo-functional alterations are the result of profound disruption of the architecture of the foot, which presents with a fallen arch secondary to the dislocation of the tarsal bones, micro- and macro-fractures due to decreased bone density and, frequently, ulcers of the midfoot. One of the pathogenic mechanisms responsible for Charcot foot is the uncontrolled increase of the blood flow secondary to sympathetic denervation. This would favour excessive bone resorption with a consequent increase in the risk of fractures, also for minimal traumas (15). Some studies have observed how patients affected by Charcot's arthropathy present with an excess of inflammatory cytokines at a local level and, in particular, of TNF-alpha and IL-1 beta. These would have the power to increase the concentration of RANKL (receptor activator of nuclear factor K-beta ligand) which, in turn, would stimulate the expression of nuclear factor kB. The latter, promoting the maturation of the osteoclasts, would be responsible for greater local bone resorption. Normally, healthy neurons secrete an osteoprotective peptide called "Calcitonin gene-related peptide" (CGRP) the effect of which is to reduce the synthesis of RANKL and thus preserve joint integrity. The role of CGRP is crucial in cases of neuropathy in which its reduced secretion has been demonstrated. In this way, the neuropathy would prompt an action favouring the development of osteoporosis secondary to local inflammation by reducing the release of CGRP (16).

Last but not least, it is important to remember how diabetic neuropathy, particularly through de-

creased tone of the sympathetic nervous system, is correlated with the deposition of calcium salts in the tunica media of arteries (Monckeberg's medial calcific sclerosis), contributing to a worsening of atherosclerotic arteriopathy, through an increase in parietal stiffness and a reduction of the vessel lumen.

Peripheral arterial disease

The salient characteristics of obstructive peripheral arterial disease in the diabetic patient as opposed to the general population are well-known: it is more frequent, it has an early onset, has a more rapid evolution and mainly involves the subpopliteal distal district. It is also important to remember that due to the concomitant sensory neuropathy, the pain symptom - the indicator for ischaemic muscle damage - may be lacking not only during the later phases of the disease when ulcers are already present, but also during the so-called "functional ischaemia" or intermittent claudication phase. For these reasons, when, in a diabetic foot, semiological signs become visible, severe peripheral arterial disease is usually already in course. The clinical characteristics of the chronically hypoperfused foot are the direct representation of the poor blood supply to the district affected: thinning skin with an atrophic, translucent appearance, through which it is possible to see the subcutaneous circulation, pale colour, low temperature, absent or hyposphygmic pulses, fragile veins, hairlessness, and dystrophic nails.

The vascular foot, moreover, becomes particularly susceptible to the formation of ulcers in a wide variety of sites although this is frequently correlated with trauma due to friction caused by footwear (sides of the foot, heel bone, back) or with poor care of the foot (area around the nails).

A typical clinical scenario of the vascular diabetic foot is also represented by gangrene of the toes and the frontal part of the foot. This can be divided into a dry form and a damp form when a suprainfection is in course. In the "blue toe syndrome", caused by the occlusion of the common digital artery, the toes first turn a purply-red colour, after which they become cyanotic and ultimately black. In absence of infective complications, the skin becomes dry and shrivelled and the toes may become mummified.

A particular aspect of atherosclerosis, which is often observed in diabetics, is Monckeberg's medial calcific sclerosis, which involves the deposition of calcium salts in the tunica media of the arteries, secondary to secondary to sympathetic denervation.

Although peripheral arterial disease is generally considered an additional risk factor for the development of ulcers, this data has not been confirmed to the same extent as that referring to neuropathy. It is well-known, on the other hand, that the presence of peripheral obliterative arteriopathy represents an important prognostic factor for amputation (17). It is also an obstacle to the treating and healing of infected lesions inasmuch as it reduces oxygenation and antibiotic release (18, 19).

Finally, it is also crucial to remember that peripheral vascular disease in the diabetic patient, as per erectile dysfunction, should not be considered merely in terms of the vascular disease of the lower limbs, but conceived of as a specific manifestation of the generalised arteriopathy typical of this patient. It is, therefore, a good idea to investigate a possible involvement of the cerebral and cardiac districts (echo-colour-Doppler of the epiaortic trunks, electrocardiogram, echocardiogram) also in the light of any therapeutic repercussions that could derive therefrom (20).

Clinical characteristics of diabetic foot infections

Ischaemia and neuropathy associated with glycometabolic failure, place patients affected by diabetic foot at a greater risk of developing infections of the superficial and deep tissue. It is well-known that diabetics present a deficit in the anti-bacterial activity of monocytes-macrophages and polymorphonuclear granulocytes. Moreover, poor tissue perfusion secondary to peripheral vascular disease brings about a reduced inflammatory response with alteration of the wound healing process. Added to this is an abnormal synthesis of collagen due to non-enzymatic glycosylation processes.

In the diabetic foot, infections can manifest themselves with clinical signs that are modest compared to a non-diabetic patient and this can lead to an erroneous underestimation of the gravity of clinical pictures that

do not appear serious but which can evolve rapidly towards destructive forms, placing the limb, or even the life of the patient at risk. This happens when the simultaneous presence of neuropathy and vascular disease, with consequent reduction of the classic signs of inflammation (in particular dolor, rubor and calor), induces the doctor and the patient to underestimate the gravity of the infective process, which can easily spread due to the immunological deficits (13, 14).

Infections of the soft tissues

Infections of the skin and adnexa are probably the most common infections in diabetic patients. Each soft tissue lesion could potentially spread throughout the limb through the plantar spaces, causing necrosis, cellulitis, phlegmons and abscesses. Necrotising skin lesions are particularly serious as they can rapidly evolve and present an elevated level of systemic toxicity with a high mortality rate.

The simultaneous presence of staphylococcal and streptococcal bacteria can generate very serious clinical scenarios of cellulitis and phlegmonosis, which can rapidly lead to widespread necrotic areas. This process is promoted by streptococcal hyaluronidase, which facilitates the spread of the necrotising toxins produced by the staphylococci. These germs are, moreover, capable of producing angiotoxins, which can cause in situ thrombosis of the vessels, potentially leading to necrosis and gangrene.

A very dangerous scenario is created by necrotising fasciitis in which the onset of the infective process is generally deep in the site of a trauma or an insect bite. The lower limbs are the parts most affected although this condition can manifest itself in any area of the skin. Initially, the signs of acute cellulitis appear with redness, swelling and intense pain, after which the affected area becomes bluish in colour and blisters appear, initially containing a yellow substance which then turns reddish-black. The infection extends rapidly along the fascial layers causing widespread necrosis. The blisters burst and skin gangrene with clean-cut edges appears (21). Patients often present with a toxic state accompanied by fever and often ketoacidosis. Generally, the aetiology is polymicrobial with a mixture of aerobic and anaerobic species.

There is a higher incidence of non-clostridial crepitant cellulitis in diabetics compared to non-diabetics characterised by the widespread presence of gas in the tissues and by dark, fetid-smelling secretions. The aetiological agents are anaerobes on their own or in association with aerobes (21).

Osteomyelitis

Osteomyelitis is a serious complication of the infected diabetic foot, being correlated with a high risk of amputation. All the bones in the foot can be affected although those most frequently involved are the small bones of the toes and the metatarsal heads. Clinically speaking, an osteomyelitic process is to be suspected when patients present with:

- slow-healing ulcers which on probing allow contact with the bone structures (probe-to-bone test);
- fever and localised pain;
- areas of perilesional osteorarefaction visible in the X-ray of the foot.

Unfortunately, radiographic findings are often non-specific inasmuch as areas of bone demineralisation may also be observed due to inflammatory osteoporosis in absence of infection. Nuclear magnetic resonance imaging of the foot provides more accurate results.

Last but not least, it is important to remember that a biopsy of the affected bone with histological and microbiological analysis is the gold standard for a correct diagnostic and therapeutic definition. But this examination too is not devoid of errors: false negatives can occur when insufficient samples are available or after treatment with antibiotics. On the other hand, false positives can occur in the case of contamination from external agents.

Therefore, the diagnosis of osteomyelitis is predominantly based on clinical findings (torpid infections, exposed or probeable bone tissue, resistance to antibiotic treatments) associated with one or more radiological alterations (19).

Bacteraemia

Bacteraemia is a serious complication for patients as it exposes them to the risk of sepsis, to the formation

of metastatic infections (such as endocarditis, cerebral abscesses, arthritis) and to disseminated intravascular coagulation phenomena with a high mortality rate. In these cases, the angioinvasive nature of the microorganisms involved comes into play, i.e. their capacity to enter the bloodstream starting from the initial site of infection (19)

Treatment of infections

Infections of the lower limbs are one of the main reasons for hospitalising patients affected by diabetes mellitus, and one of the main factors leading to the potential amputation of a limb. The inflammatory picture can present in various ways; in particular, clinically there is a tendency to distinguish between minor infections, in which the lower limb is not at imminent risk of amputation, and more serious infections in which the potential risk of losing the limb effectively exists.

The more minor infections are usually distinguished by superficial ulcers, without significant signs of ischaemia, and the lesion does not penetrate down to the deeper layers. In these cases, the perilesional cellulitis does not extend by more than 2 cm from the initial site of infection. These patients are usually clinically stable, and do not show signs of systemic involvement.

However, moderate-to-severe infections, which can place the limb at risk, normally present with perilesional cellulitis, which extends by more than 2 cm from the entry portal, in presence of systemic clinical manifestations such as fever, localised swelling, lymphangitis, hyperglycaemia, leukocytosis, and increased inflammation markers. In addition to the above, also the presence of signs at a local level, such as purulent secretions, fetid odour, gangrene or necrosis are indications of severe infection. It is important to underline how, in some cases, in diabetic patients with infections in the advanced stages, the above signs and symptoms might not be evident due to a reduced inflammatory response linked to conditions of peripheral neuropathy or ischaemia: in fact, not only do many patients not report pain, but neither do they present with fever or leukocytosis, or increased ESR or CRP, even in clinical pictures characterised by severe infections (22). The gravity of the infection determines the need for admission to hospital, the choice of the antibiotic to be administered, the administration route and the duration of the treatment. Culture samples can be a useful guide in determining the type of antibiotic treatment to be adopted, but various studies demonstrate that the only useful samples are those taken from the deep tissues, obtained aseptically during debridement or a surgical procedure. Swabs from superficial wounds can be full of contaminants and misleading for the choice of the correct therapy. Often the infection to be investigated is polymicrobial, and if several organisms are isolated, the policy is not to direct the therapy at the less virulent bacteria, such as enterococci, coagulase-negative staphylococci or corynebacteria. *Staphylococcus aureus* is the most virulent and most frequently isolated pathogen, but beta-hemolytic streptococci, or other Gram-positive germs are also found. In patients with previously treated infections, it is possible to isolate enterobacteria or Gram-negative cocci or multi-resistant microorganisms such as S. aureus MRSA or enterococci resistant to vancomycin. Chronic wounds can present various bacterial species, including Pseudomonas aeruginosa, in particular in patients in mild climate zones and in subjects treated with hydrotherapy or frequent exposure of the skin to water. Finally, anaerobic pathogens are the most frequent in wounds with ischaemic necrosis or in those that attack the deep tissues. These pathogens are rarely the only ones and often form part of polymicrobial infections (23-25).

Treatment with antibiotics

As is well-known, international guidelines repeatedly stress the concept of not treating non-infected wounds with antibiotics (IDSA) (26) (Tab. 1).

Infected wounds must be treated with specific local medicaments, in association with antibiotic therapy, but first and foremost debridement must be performed and, if required, a surgical procedure in the case of deep widespread infections of the soft tissues, abscesses with compartment syndromes or in the presence of necrotic tissue. Last but not least, for rapid healing of the wounds, optimal glycaemic control and sufficient vascularisation are of fundamental importance.

Table 1. Suggeted empiric antibiotic regimens based on clinical severity for diabetic foot infections[a]

Infection Severity	Probable Pathogen (s)	Antibiotic Agent	Comments
Mild (usually treated with oral agent[s])	Staphylococcus aureus (MSSA); Streptococcus spp	Dicloxacillin	Require QID dosing; narrow spectrum; inexpensive
		Clindamycin[b]	Susually active against community-asso-ciated MRSA, but check macrolide sensitivity and consider ordering a "D-test" before using for MRSA. Inhibits protein synthetis of some bacterial toxins
		Cephalexin[b]	Requires QID doisng; inexpensive
		Levofloxacin[b]	Once daily dosing: suboptimal Against S. Aureus
		Amoxicillin-clavulanate[b]	Relatively broad spectrum oral agent that includes anaerobi coverage
	Methicillin-resistant	Doxycycline	Active agains many MRSA & some gram-negatives; Uncertains against streptococcus species
		Trimeth orpim/sulfamethoxazole	Active agains many MRSA & some gram-negatives; Uncertains activity against streptococci
Moderate (may be treated with oral or initial parenteral agent[s]) or severe (usually treated with parenteral agent[s])	MSSA; Steptococcus spp; Enterobacteriaceae; obligate anaerobes	Levofloxacin[b]	Once-daily dosing; suboptimal against S. aerosu
		Cefoxitin[b]	Second genertori oephalossporin with anaerobic converage
		Ceftriaxone	Oncedaily dosing, third-generation Cephalosporin
		Ampicillin- sulbactam[b]	Adequate if low suspiction of P. aeruginosa
		Moxifloxaci[b]	Once-daily oral dosing. Relatively broad-spectrum, including mosts obligate anaerobic organism
		Ertapenem[b]	Once-daily oral dosing. Relatively broad-spectrum, including anaerobes, but not active against P. aeruginosa
		Tygecycline[b]	Active agains ;RSA. Spectrum may be excessilvely broad. Hig rates of nausea and vomiting and incresed mortality warning. Nonequivalent to ertapenem + vncomycin in 1 randomized clinical trial
		levofloxacin[b] or ciprofloxacin[b] withclindamycin[b]	Limited evidence supporting clindamycin for severe S. Aureus infection; PO & IV formulations for both drugs
		Imipenem-cilastatin withclindamycin[b]	Very broad-spectrum (but not agains MRSA); use only when this is required. Consider when ESBL-producing pathogens suspected

(continued)

Table 1. Suggeted empiric antibiotic regimens based on clinical severity for diabetic foot infections[a]

Infection Severity	Probable Pathogen (s)	Antibiotic Agent	Comments
	MRSA	Linezolid[b]	Expensive; increased risk of toxicities when used >2 wk
		Deptomycin[b]	once-daily dosing. Requires serial monitoring of increasing
		Vancomycin[b]	Vancomycin MICs for MRSA are gradually increasing
	Pseudomonas aeruginosa	Piperacillin-tazobactam[b]	TID/QID dosing. USeful for broad-spectrum coverage. P. aerruginosa is an uncommon pathogen in diabetic foot infections except in special circumstances (2)
Infection severity	Probable Pathogen(s)	Antibiotic Agents	Comments
	MRSA, enterobacteriacae, Pseudomonas, and obligate anaerobes	Vancomycin[c] plus one of the following; ceftazidime, cefepime, piperacillintazobactam[b], aztreonam[b], or a cabapenem[b]	Very broad-spectrum coverage; usually only used for empiric therapy of severe infection. Consider addition of obligate anaerobe coverage if ceftazidime, cefpime, or aztreonam selected

Agents in boldface type are those that have been most commonly used as comparators in clinical trials (see Table 7). The only agents currently specifically FDA approved for diabetic foot infections are shown in italics.

Narrow-spectrum agents (eg, vancomycin, linezolid, daptomycin) should be combined with other agents (eg, a fluoroquinolone) if a polymicrobial infection (especially moderate or severe) is suspected.

Use an agent active against MRSA for patients who have a severe infection, evidence of infection or colonization with this organism elsewhere, or epidemiological risk factors for MRSA infection.

Select definitive regimens after considering the results of culture and susceptibility tests from wound specimens, as well as the clinical response to the empiric regimen.

Similar agents of the same drug class can probably be substituted for suggested agents.

Some of these regimens do not have FDA approvai for complicated skin and skin structure infections.

Abbreviations: CPK, creatine phosphokinase; ESBL, extended-spectrum b-lactamase; FDA, US Food and Drug Administration; IV, intravenous; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-sensitive Staphylococcus aureus; PO, oral; QID, 4 times a day; TID, 3 times a day.

[a] *Agents approved for treating skin and skin structure infections on the basis of studies that excluded patients with diabetic foot infections (eg, ceftaroline, telavancin) are not included.*

[b] *Agents shown to be effective in clinical trials including patients with diabetic foot infections.*

[c] *Daptomycin or linezolid may be substituted for vancomycin.*

In connection with the choice of treatment, the two possible situations likely to arise are as follows.

In the case of a superficial wound, or a moderate infection, as already mentioned, without systemic symptoms, hospitalisation is not necessary and antibiotic therapy by oral route is normally sufficient. Therapy should be started as soon as possible, and with drugs that offer adequate cover against Gram-positive microorganisms, with a narrow spectrum (amoxicillin-clavulanic acid, cephalosporin, fluoroquinolones, doxycycline). Usually after 3-5 days, an initial clinical response is observed with improvement of inflammation; if this were not the case, it would be advisable to re-evaluate the wound with the possibility of adjusting the initial therapy, particularly if culture examinations are available, formulating it on the basis of the antibiogram. The therapy normally lasts for a total of 1-2 weeks.

For severe infections, that is, in the presence of systemic symptoms, the antibiotic therapy should be administered by parenteral route, and therefore, hospitalisation is recommended. Once the patient is clinically stable, the transition to therapy by oral route may be made. Often in these cases there is involvement of the deep tissues, with clinical signs such as

oedema, lymphangitis, soft tissue necrosis, gangrene and/or osteomyelitis. An X-ray should be carried out to exclude bone involvement and to assess the possible presence of gas. If septicaemia is suspected, it is useful to take samples for haemoculture. The metabolic and nutritional state of the patient must be fairly good in order to guarantee more rapid healing of the wounds. In this case, antibiotic therapy will be a wide spectrum treatment, using several drugs (ampicillin-sulbactam piperacillin-tazobactam, ceftazidime-clindamycin,cef otaxime+clindamycin, fluoroquinolone+clindamycin, vancomycin+levofloxacin+metronidazole, meropenem, linezolid, tigecycline).

Usually the antibiotic therapy lasts for 2-4 weeks.

Last but not least, a multidisciplinary approach should be considered for the evaluation of the vascular structure and the possible need for a surgical operation (even conducted in various stages), for the draining of abscesses and/or amputation. The taking of bone tissue or deep tissue samples can be very useful in these cases for the preparation of appropriate microbiological cultures.

The factors that normally prognosticate healing are the absence of exposed bone, a palpable popliteal pulse, toe pressure >45 mmHg, ankle pressure > 80 mmHg, a peripheral white blood cell count <12000/mmc and a transcutaneous pressure of O2 > 40 mmHg. Patients who have had an infection in the past are at risk of recurrences in the course of a few years, so effective education on the subject of prevention is of vital importance (27-31).

Peripheral arterial disease: diagnostic-therapeutic approaches

The prevalence of peripheral arterial disease (PAD) in subjects affected by diabetes is high: from 10 to 40% depending on the definitions used (32-36). The incidence is correlated with smoking, hypertension, age, HbA1c value, and it is calculated that for every 1% increase in HbA1c there is a corresponding 26% increase in the risk of PAD (34, 37, 38).

Peripheral arterial disease (PAD), involving a greater risk of amputation, is the most important factor after the revascularisation processes (39, 40).

So in the case of foot lesions, the questions to ask, in addition to verifying for the possible presence of infection, are:

- is there concomitant peripheral obliterative arteriopathy?
- Is there critical ischaemia of the lower limb? (defined by TcPO2 ≤10 mmHg on the back of the foot without any increases following the inhalation of oxygen, or ankle pressure ≤30 mmHg in absence of arterial calcifications with evidence of gangrene, or pain at rest requiring analgesics lasting more than two weeks).

Non-invasive examinations of the arterial district of the lower limbs include, in addition to the physical examination of the peripheral pulses, segmental Doppler pressures of the ankle / arm (ABI = ankle-brachial indices), positive if < 0.9, but it should also be taken into account that it could appear falsely elevated if the rear tibial artery is incompressible due to calcification of the tunica media, the measurement of transcutaneous oxygen pressure (TcPO2,) which if < 30-40 mmHg, prognosticates difficult healing of the ulcer (41), echo-colour-Doppler ultrasound to explore the proximal and distal arterial circulation. But even if these non-invasive vascular tests do not give clearly pathological results, it is essential to consider an angiography if the foot ulcer fails to heal after 6 weeks of optimal treatment (35, 39).

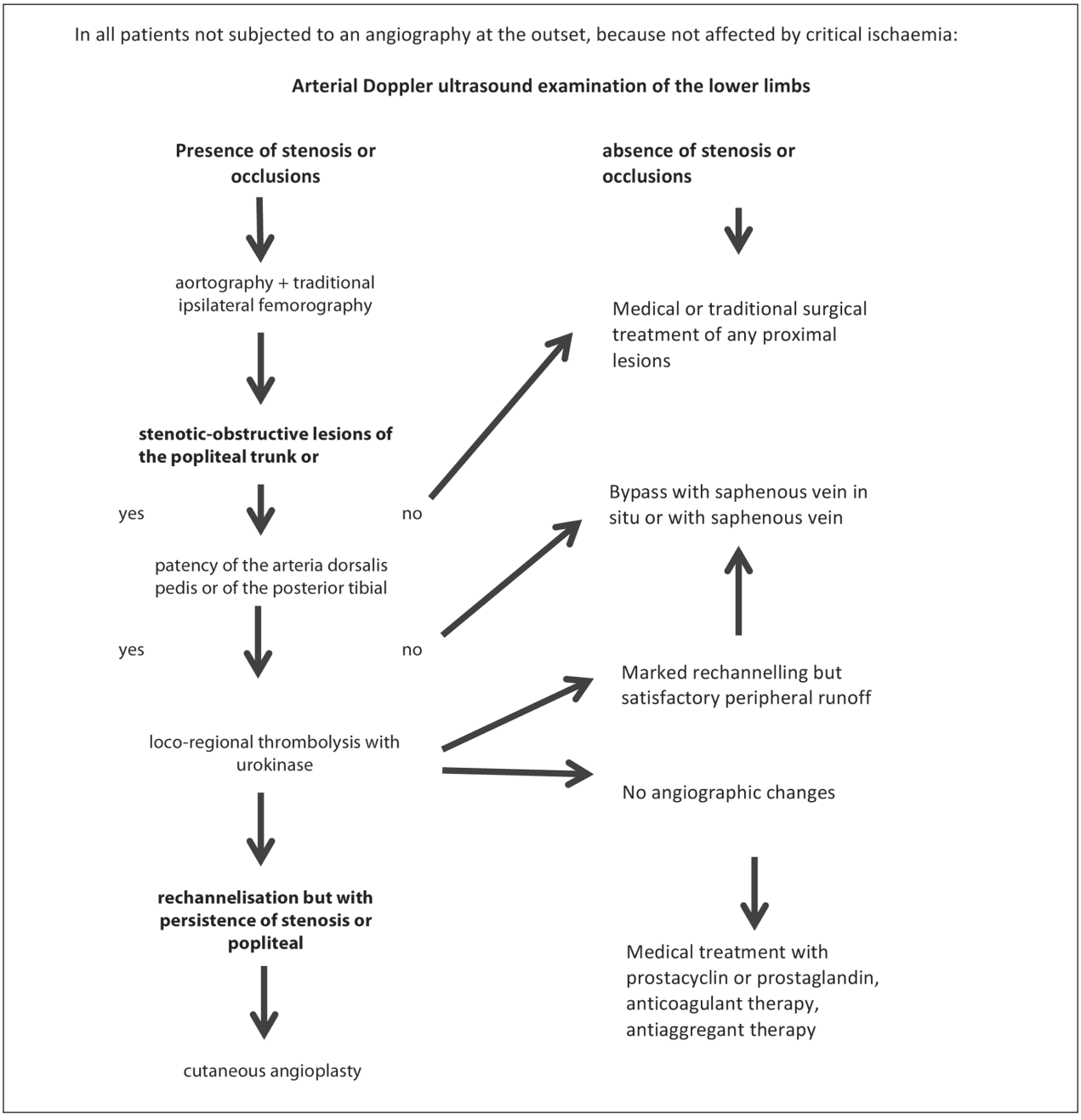
If a critical ischaemic state is in course, the wounds will not heal unless revascularisation is performed. Therefore, there is an indication to immediately conduct an aortography+ipsilateral femorography with an examination of the circulation of the foot (42, 43). In most centres, the angiography of the lower limbs is carried out using Seldinger's technique, after careful rehydration in order to reduce the risk of contrast nephropathy. This investigation may be replaced by or integrated with an MRA or CT angiography (35, 44). The MRA evaluates the aortoiliac flow very well and is recommended first and foremost if an overview of the arterial axis is required. CT angiography, on the other hand, examines the arterial wall, therefore it is important when planning endovascular revascularisation strategies or tactics (e.g. subintimal angioplasty) becomes necessary, even though the sensitivity of the subpopliteal district is still inferior to that of the angiography (43).

The restoration of arterial circulation, a priority in the case of critical ischaemia, can be achieved through:

1. endoluminal methods: a) percutaneous transluminal angioplasty (PTA) with the application of a stent, b) loco-regional thrombolysis, possibly followed by angioplasty; 2. open procedures: a) bypass with saphenous vein in situ or saphenous vein inverted or with biological materials or synthetic alternatives (with poorer long-term patency results), if the peripheral run-off is sufficient, b) thromboendarterectomy.

Table 2 illustrates the flow chart of our approach to patients with ulceronecrotic lesions of the foot and PAD.

Table 2. ??????????????????????????



Attempts to salvage a Iimb affected by diabetic gangrene through loco-regional thrombolysis with urokinase, used primarily in the '90s, should be reserved for cases with ulceronecrotic lesions at least 4 weeks old. Beyond this period, the natural history of the lesion does not seem affected by the method probably due to the incapacity of the drug to lyse the "older" thrombi which also obstruct the vessels of the collateral circulation (45).

The use of pharmacological therapy to maintain patency after revascularisation is still controversial but antiaggregant treatment is used by most of the authors (43, 20). In order to maintain the patency of the grafts, numerous studies confirm the efficacy of ASA (Grade 1A) (46) and ticlopidine (Grade 1B). Definitive data on clopidogrel is not yet available and the policy of our centre is to follow current guidelines which recommend: infrainguinal bypass with autologous vein or prosthetic material and ASA, distal bypass with vein ASA; bypass with a high occlusion risk (poor run-off, venous channel not optimal, femorodistal bypass) and antivitamin K+ASA. In order to maintain arterial patency after the endovascular procedure, some studies show favourable results with long-term ASA (Grade 1C) (47); sufficient data is not yet available to demonstrate the safety and efficacy of ASA+copidogrel; in any case, with regard to favourable reports on coronary circulation, it is reasonable to envisage this association in the medium term after a surgical procedure on smaller calibre vessels (48, 49). In our clinical practice, after PTA with or without stenting of the iliac artery and ASA, of the femoral artery, popliteal artery and subpopliteal district ASA+ticlopidine or ASA+clopidogrel; in the 24 h after surgery continuous infusion of Iloprost 0.05 mg to reduce the risk of early reocclusion (50).

Lumbar sympathectomy is considered to be an obsolete procedure for the treatment of critical ischaemia of the lower limbs in patients with diabetes mellitus (35).

In cases in which revascularisation through surgery or interventional radiology proves to be impossible, or in the event of failure, an infusion of prostacyclin can be effective, at least in the short term (43). The drugs validated for the treatment of critical ischaemia are the prostanoids Iloprost (PGI2) and Alprostadil (PGE1) and some scientific associations (ESC, EASD) recommend - with evidence level A - treating patients affected by critical ischaemia and not susceptible to revascularisation with infusions of prostanoids (48).

In addition to prostanoid infusions, conservative therapy of foot lesions with non-revascularisable critical ischaemia also envisages pain sedation, improvement of the skin lesions and prolonging life by effectively combining various therapeutic options: centrally-acting analgesics, epidural analgesia especially in cases of painful medicaments, medullary electrostimulation and the treatment of deep and soft tissue infections (20).

Major and minor amputations

Poor tissue repair, persistent inflammation, the presence of deep abscesses, osteomyelitis and systemic involvement can lead to a very serious, clinical picture of gangrene or necrosis, which from being localised can extend widely, requiring minor or major amputation surgery in order to radically remove the infected tissue.

The same risk factors that predispose to the development of an ulcer can also be considered potential causes predisposing to amputation, albeit with a number of differences. Peripheral arterial disease, for example, which is often but not always associated with the development of lesions of the lower limbs, as already mentioned, proves to be a significant element of risk for amputation surgery. However the main risk factors for the development of gangrene and hence amputation are many and varied, and are shown in table (Tab. 3). It is important to point out how poor glycaemic control can be the cause common to the development and progression of many of the abovementioned risk factors: peripheral arterial disease, microangiopathy, alterations of the microcirculation, altered phagocytic capacity of leukocytes, glycosylation of tissue proteins, which contribute to the formation of ulcers of the lower limbs, delay tissue repair processes and favour the evolution towards amputation.

Amputations of the lower limbs fall into two categories: *major* and *minor*. As a general rule, the more distal an amputation and the less the loss of load, stability and mobility, the more cardiopulmonary stress is reduced. However, surgery must be carried out in such a

Table 3. The main risk factors for the development of gangrene and hence of amputation

- peripheral arterial disease
- presence of diabetic neuropathy
- infection
- past personal history of amputation of a lower limb
- deformity or osteostructural alteration of the foot
- trauma
- Charcot foot
- altered visual perception
- poor glycaemic control
- advanced age
- male sex
- race (particularly black and Hispanic)

way that the part remaining can still support the weight and allow the use of a prosthesis, orthesis, or of special footwear especially designed to guarantee walking.

The level of amputation should be chosen to allow good postoperative recovery, but at the same time, the general conditions of the patient must be taken into consideration.

Good tissue perfusion is the best condition for the scar healing process during the postoperative period, therefore, pre-operative assessment of the patient's vascular structure must be performed: if ankle pressure is less than 50 mm Hg or transcutaneous oxygen pressure (TcPO2) is less than 30 mmHg, the probability of successful healing after the amputation of a toe or of the forefoot is very low (51-54).

Minor amputations (transmetatarsal amputation or distal amputations)

Amputations are classed as minor when they are entirely limited to the foot, including amputation-disarticulation at tibiotarsal level.

Depending on the site of the foot involved in the procedure, they are classed as:

1) *Amputations of the forefoot*: end of the great toe, great toe, first ray, small toes, central rays, external rays (V ray), transmetatarsal;
2) *Amputations of the midfoot*: Chopart level and its variants;
3) *Amputations of the rearfoot*: calcanectomy, disarticulation of the subtalar joint, amputation-Syme disarticulation, osteoplastic amputations.

An amputation wound is closed by first intention when the tissue is free from infection and well-perfused. Open amputations are required when the tissue is infected and necrotic. It is often possible to salvage important load areas by performing a limited resection with the management of an open ulcer. In the case of extended, deep ulcers, skin grafts or reconstructive plastic surgery may be considered, also with tissue transplantation. During the initial postoperative phase, for effective and rapid healing it is vital not to load weight onto the limb, to continue with appropriate antibiotic therapy, and to guarantee optimal metabolic control and appropriate food intake.

In some cases, the part affected by gangrene spontaneously detaches itself (auto-amputation); this normally happens when the lesion has been present for several months and the tissue is ischaemic. Experts are favourable to surgical resection of the gangrene each time joints or tendons are involved, provided that the arterial supply is sufficient for the healing of the lesion.

Last but not least, minor amputations do not significantly impair walking, which can be facilitated with the aid of a pair of therapeutic shoes or an orthosis. A greater predisposition towards the development of deformities may however occur, with a consequent increase in the risk of further ulcers and new amputations; for this reason, strict controls are essential throughout the patient's life and special attention must be paid to footwear, which may have to be modified or, in certain cases, made to measure (55).

Major amputations (proximal with respect to the metatarsal joint)

Severe ischaemia of the leg that cannot be revascularised is the primary reason for amputating the lower part of the leg. Prior to proceeding with surgery, however, an attempt at revascularisation is always considered.

The main risk factors for major amputation are: old age, female gender, visual limitation and wide spreading of the ulcers.

These operations are associated with a high mortality rate and a significant risk of the loss of walking ability. A non-curable ulcer is not an indication for a major amputation. A major amputation is carried out in the presence of intense uncontrolled pain at rest or progressive necrosis of the tissues, with impossibility to perform revascularisation. Other indications are severe and progressive infections of the foot, in a leg without a significant arterial disease, with or without sepsis, which cannot be controlled by debridement and by conservative treatment, or clinical pictures characterised by serious neuro-osteoarthropathic deformities (56).

To facilitate rehabilitation it is very important to preserve the knee.

Types of major amputation operations practised:
- transfemoral;
- transcondylar;
- disarticulation of the knee;
- transtibial.

Transfemoral amputation is usually indicated for patients in generally poor conditions, in which large wounds with complications cannot be tolerated. A disarticulation of the knee should be considered in patients who have ankylosis of the knee or who are bedridden or seriously disabled.

The decision of the level of amputation normally depends on the possibility of postoperative healing, defined on the basis of techniques for measuring tissue perfusion (TcPO2, laser-doppler, popliteal doppler). The postoperative mortality rate is higher in cases of transfemoral amputation (10-40%) compared to transtibial amputation (5-20%).

After surgery, patients must be subjected to a personalised rehabilitation programme for postural re-education and for instructions on the use of the prosthesis.

Since, as already mentioned, patients undergoing major amputations are subjected to a high risk of a further contralateral amputation, a monitoring programme for the remaining foot is of fundamental importance, keeping in mind that, from the little data currently available, the long-term survival of this type of patient is, in any case, rather low (in certain cases life expectancy < 40% after 3 years) (17, 56).

Hyperbaric oxygen therapy (HBOT) in the treatment of diabetic foot

This is a method that exploits the solubility of oxygen in plasma and which radiates to the tissues irrespective of the haemoglobin level. Even for short-lasting treatments, the O2 tension levels remain high for several hours after exposure. The oxygen is administered at high concentrations (100%) by inhalation at an atmospheric pressure greater than that at sea level. The rationale of the method is based on a number of mechanisms:
- greater deposition of neocollagen for increased speed of hydroxylation of proline and lysine residues in procollagen;
- increased proliferation of fibroblasts;
- increased production of angiogenic substances by macrophages;
- exaltation of leukocyte phagocytosis (increased bactericidal action against aerobes);
- direct bactericidal action against anaerobes);

Not many papers have been published on HBOT in the treatment of diabetic foot but over the past years there have been numerous reports on the healing of ulcers in patients with arterial disease and diabetes, as proven by the Cochrane review (1).

The HBOT indications followed by our centre for this particular disease, also on the basis of other data (2) are:
- anaerobic infections;
- widespread infections of the soft tissues and/or osteomyelitis;
- patients with class III, IV and V lesions according to Wagner's ulcer classification if the pO2tc in the vicinity of the ulcer is < 30 mmHg. Hyperbaric oxygen therapy is however to be considered as an additional treatment and not as a substitute for other therapies (57-59).

Negative pressure therapy and other advanced therapies

Negative pressure therapy or VAC-therapy (Vacuum-Assisted Closure) consists of the application of a subatmospheric pressure on the surface of the wound. This technique stimulates the healing of the lesions

through an increase in tissue perfusion, reduction of the oedema and the bacterial load and stimulation of the granulation tissue. Randomised studies have demonstrated that VAC therapy has the power to reduce the healing time of the ulcers and post-surgery wounds of diabetic foot, thereby reducing length of stay in hospital, rate of hospitalisation and consequently healthcare costs (60).

Other advanced therapies are fundamentally represented by dermoepidermal equivalents and skin substitutes which, applied by expert personnel, ensure more rapid healing of the lesions. Use is also made of gels formulated with platelet-derived growth factors (PDGF) with the power to stimulate neoangiogenesis and cell proliferation, and with epidermal growth factors (EGF) (61-64).

Prevention

A number of studies have demonstrated that a regular examination of the feet, stratification of risk and education of the patient can contribute to reducing the emergence of foot lesions in at least 50% of patients (65).

The role of the diabetologist is to identify patients at high risk in order to include them in an education programme and monitor them closely (66). The risk factors identifiable through clinical examination and the taking of medical history are:

- previous ulcers/amputations;
- impairment of sensitivity (monofilament test
- impairment of perception of vibration;
- absence of Achilles reflex;
- social problems;
- IQ below normallimits;
- deformity of the toes or calluses if associated with peripheral vascular disease or peripheral neuropathy;
- inappropriate footwear.

On the basis of the risk assessment, various levels of intervention are indicated (Tab. 4).

The routine care of the foot (cutting of toenails and removal of calluses) should be carried out by an expert podologist, and specialised orthopaedic personnel should make suitable footwear and arch supports designed to off-load pressure from the areas at risk (67, 68), particularly in the forefoot (69).

The most effective educational approach is most probably a combination of active learning with audiovisual readings and classroom lessons both one-to-one and in groups (66).

Table 4. On the basis of the risk assessment, various levels of intervention are indicated

Risk level	Type of intervention
Category 0	
- has satisfactory sensitivity	- visit to the podology outpatients' clinic at least once a year
- does not have ulcers	- education of the patient, also regarding choice of footwear
- possible deformities of the foot	
- has a disease that could lead to insensitivity	
Category 1	
- does not have sufficient peripheral sensitivity	- suitable footwear
- does not have plantar ulcers	- soft insoles
- does not have deformities of the foot	- podology check-up every six months
- plantar pressure >500KPascal on the podobarograph during walking	
Category 2	
- does not have sufficient peripheral sensitivity	- podology check-up every 3 months
- does not have plantar ulcers	- insoles prepared on the basis of the imprint
- has a deformity of the foot	- prescribing of suitable shoes
- plantar pressure >1000KPascal on the podobarograph during walking	

Conclusions

The evolution of medical disciplines has made it possible to create favourable conditions to reduce the number of major amputations and guarantee effective organisation involving various different professional figures (diabetologist, vascular surgeon, orthopaedic surgeon, interventional angio-radiologist, plastic surgeon, podologist, specialised nurse, orthopaedic technician), who, on the basis of their individual competencies, take care of and educate patients and their families and can really make it easier to prevent the complications of diabetic foot or salvage a limb affected by diabetic gangrene.

References

1. Boulton AJ, Vileikyte L,Regnarson-Tennvall G, Apelqvist J. The global burden of diabetc foot disease. Lancet 336: 1719-1724; 2005
2. McNeely MJ, Boyko EJ, Ahroni JH, Stensel VL, Reiber GE, Smith DG, Pecoraro RF. The independent contributions of the diabetic neuropathy and vasculopathy in foot ulceration. Diabetes Care 18: 216-219; 1995
3. International Diabetes Federation and International Group on the Diabetc Foot. Diabetes and Foot Care. Time to Act, International Diabetes Federation, Brussel, 2005
4. Margolis DI, Allen-Taylor I, Hoffstad O, Berlin JA. Diabetic neuropathic foot ulcers and amputation. Wound Repair Regen 13: 230-236; 2005
5. Frykberg RG. Epidemiology of the diabetic foot: ulceration and amputations. Adv Wound Care 12:139-141; 1999
6. Centers of Disease Control and Prevention. National diabetes fact sheet: general information and national estimates on diabetes in United States. Centers for Disease Control and Prevention. Atlanta 2005
7. American Diabetes Association. Diabetes. 1996 Vital Statistics, American Diabetes Association. Alexandria VA 1996
8. Lavery LA, Ashry HR, van Houtum W, Pugh JA, Harkless LB, Basu S. Variation in the incidence and proportion od dieabetes-related amputations in minorities. Diabetes Care 19: 48-52; 1996
9. Moss SE, Klein BEK. The prevalence and incidence of lower extremity amputation in a diabetic population. Arch Intern Med 152: 610-616; 1992
10. Bakker K, van Houtum W, Riley PC. The International Diabetes Federation focuses on the diabetc foot. Curr Diabetes Rep 5: 436-440; 2005
11. Eskeelisen E, Eskelisen A, Alback A, Lapantalo M. Major amputation incidence decreases both in non-diabetic and diabetic patients in Helsinki. Scand J Sug 95: 185-189; 2006
12. International Diabetes Federation, Diabetes Atlas, third edition, Brussel 2007
13. Monti M. "L'ulcera cutanea. Approccio multidisciplinare alla diagnosi ed al trattamento" Springer 2000b.
14. "Diabetic foot disorders. A clinical practice guideline" Supplement of The Journal of Foot & Ankle Surgery 2006
15. Papanas N. et al. "Etiology, pathophysiology and classifications of the diabetic Charcot foot" Diabetic foot and ankle 2013,4
16. Liping W. et al. "Calcitonin gene-related peptide stimulates stromal cell osteogenic differentiation and inhibits RANKL induced NF-Bactivation, osteoclastogenesis and bone resorption" Bone. 2010 May ; 46(5): 1369–1379
17. Tsourdi E. et al. "Current aspects in the pathophysiology and treatment of chronic wounds in diabetes mellitus" BioMed Research International, Volume 2013
18. Lipsky B. A. et al "2012 Infectious diseases society of America Clinical practice guideline for the diagnosis and treatment of diabetic foot infections" Clinical infectious diseases 2012;54(12): 132-173
19. Lipsky B.A. "Medical treatment of diabetic foot infections" Clinical infectious diseases 2004:39 (Suppl 2)
20. Mollo PE, Di Salvo MM, Failla G, Marcoccia A, Mosti G, Guarnera G. Ulcera Ischemica e Ischemia Critica. Documento di posizionamento AIUC. Acta Vulnologica 10, n. 4, p 215-216. 2012
21. Fitzpatrick T.B. et al. "Atlante di dermatologia clinica" 5° edizione, McGraw Hill 2006
22. Edelson GW, Armstrong DG, Lavery LA, Caicco G. The acutely infected diabetic foot is not adequately evaluated in an inpatient setting. Arch Intern Med 1996; 156: 2373-8
23. Lipsky BA, Pecoraro RE, Wheat JL. The diabetic foot: soft tissue and bone infection. Infect Dis Clin North Am 1990; 4:409-32
24. Lipsky BA. Evidence-based antibiotic therapy of diabetic foot infections. FEMS Immunol Med Microbiol 1999; 26: 268-76
25. Hauser CJ, Tissue salvage by mapping of skin surface transcutaneous oxygen tension index. Arch Surg 1987; 122:1128-30
26. IDSA Guidelines, 2012 Infectious Diseases Society of America Clinical Practice Guideline for the Diagnosis and Treatment of Diabetic Foot Infection
27. Armtrong DG, Liswood PJ, Todd WF, William J, Stickel BronzeAward. Prevalence of mixed infections in the diabetic pedal wound. A retrospective review of 112 infections. J Am Podiatr Med Assoc 1995; 85:533-7
28. American Diabetes Association. Consensus Development Conference in Diabetic Foot Wound Care. Diabetes Care, 22: 1354. 1999
29. Gibbons GW, Eliopoulos GM, Infection of the diabetic foot . Management of Diabetic Foot Problems p121, edited by GP Kozak, DR Cambell , RG Frykberg, and GM Habershaw, WB Sauders, Philadelphia 1995
30. Falanga V , Wound healing and its impairment in the diabetic foot. Lancet 366: 1736-1743, 2005

31. Hartemann-Heurtier, Ha Van G Danan JP, Kosas F, Jacqueminet S, Golmard JL, Grimaldi A. Outcome of severe diabetic foot ulcers after standardised management in a specialist unit.Diabetes Metab 28:477-484, 2002
32. Adler AI, Stevens RJ, Neil A, Stratton IM, Boulton AJ, Holman RR. UKPDS 59: hyperglicemia and other potentially modifiable risk factor for peripheral vascular disease in type diabetis. Diabetes 25: 894-899; 2002
33. Williams DT, Harding KG, Price P. An evaluation of the efficacy of metod used in sceening for lower-limb arterial disease in diabetes. Diabetes Care 28:2206-2210; 2005
34. Selvin E, Wattanakit K, Steffes MW, Coresh J, Sharrett AR. HbA1c and peripheral arterial disease in diabetes: the Atherosclerosis Risk in Communities study. Diabetes Care 29: 877-882; 2006
35. International Consensus on the Diabetic foot and pratical guidelines on the management and prevention of the diabetic foot. By the International Working Group on the Diabetic Foot 2007
36. Chantelau E, Lee KM, Jungblut R. Association of the below-knee atherosclerosis to medial arterial calcification in diabetes mellitus. Diabetes Res Clin Prat 29 : 169-172; 1995
37. Beks PJ, Mackaay AJ, de Neeling JN, de Vries H, Bouter LM, Heine RJ. Peripheral arterial disease in relation to glycaemic level in an elderly Caucasian population: the Hoorn study. Diabetologia 38: 86-96; 1995
38. UKPDS
39. Faglia E, Mantero M, Caminiti M, Caravaggi C, De Gliglio R, Pritelli C, Clerici G, Graziani L et al. Estensive use of peripheral angioplasty, particulary infrapopliteal, in the treatment of ischaemic foot ulcers: clinical results of a multicentric study of 221 consecutive diabetic subjects. J Inter Med 252: 225-232; 2002
40. Adam DJ, Beard JD, Cleveland T, Bell J, Brandbury AW, Storkey H et al. BASIL trial participants. Bypass versus angioplasty in severe ischaemia of the leg: multicentre, randomised, controlled trial. Lancet 34: 366: 225-234; 2005
41. Kalani M, Brismar K, Fagrel B, Ostergren J, Jonesskog G. Transcutaneous oxygen tension and toe blood pressure as predictor for outcome of diabetic ulcers. Diabetes Care 22: 147-151; 1999
42. Hingorani A, Ascher E. Diabetic Foot: Lower Extremity Arterial Disease and Limb Salvage. Ed by AN Sidawy, Lippincot Williams and Wilkins. Philadelphia 2006
43. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fpwkes FG: on behalf of the TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 45 (suppl S): S5-S67; 2007
44. Andreozzi GM, Arpaia G, Martini R. Procedura diagnostiche e terapeutiche per il management del paziente con arteiopatia diabetica. Rivista S.I.M.G. 2: 40-70; 2010
45. Ugolotti U, Banchini E, Larini P, Marcato C, Puccianti F, Tardio SM et al. Lower Limb Critical Ischaemia in Diabetes: role of Interventional Radiology; Results of a Preliminary Experience. The Med J Sur and Med 2: 139-143; 1994
46. Cockrane 2003
47. Koppensteiner 2006
48. Clagget P, Sobel M, Jackson MR, Lid GYH, Tangeldel M, Verhaeghe R. Thrombolytic Therapy Conference on Antithrombotic and Occlusive Disease. The seventh ACCP Antithrombotic Therapy in Periferal Arterial. Chest 126: 609-626; 2004
49. Sobel M, Verhaeghe R. Antitrpombotic Therapy for Peripheral Artery Occlusive Disease. American College of Chest Physician evidence-based clinical practice guidelines. Chest 133, 815S; 2008
50. Testo Atlante di Patologia Vascolare p 259-262: ed Rossetti A., Mattioli 1885; Fidenza 2011
51. American Diabetes Association. Diabetes 1996. Vital Statistics, American Diabetes Association, Alexandria VA, 1996
52. Lavery LA, Ashry HR, van Houtumn W, Pugh JA, Harkless LB, Basu S. Variation in the incidence and proportion of diabetes-related amputations in minorities. Diabetes Care 19:48-52, 1996
53. Pecoraro RE, Reiber GE, Burgess EM. Pathways to diabetic limb amputation: basis for prevention. Diabetes Care 13:513-521, 1990
54. Caputo GM, Cavanagh PR. Ulbrecht JS, Gibbons GW, Karchner AW. Assessment and management of foot disease in patients with diabetes. N Engl J Med, 331: 854-860, 1994.
55. Albreksten SB, Henriksen BM, Holstein PE. MInor amputations on the feet after revascularization for gangrene. A consecutive series of 95 limbs. Acta Orthop Scand. 1997; 68: 291-293
56. Documento di Consenso Internazionale sul Piede Diabetico (Terza Edizione 2010)
57. Kranke P, Bennett M, Roeckl-Wiedmann I, Debus S. Hyperbaric oxygen therapy for chronic wounds. Cochrane database Syst Rev 2:CD004123; 2004
58. Fife CE. Hyoerbaric oxygen therapy applications on woud care. In Wound care practice. 2nd ed Flagstell, AZ: Bets Publishing Company p 661-676; 2004
59. Londhal M, Ossigeno terapia iperbarica come trattamento aggiuntivo delle ulcere del piede diabetico, Med Clin North Am, 2013, 97(5): 957-980
60. Nather A1, Chionh SB, Han AY, Chan PP, Nambiar A.Effectiveness of vacuum-assisted closure (VAC) therapy in the healing of chronic diabetic foot ulcers. Ann Acad Med Singapore. 2010 May;39(5):353-8.
61. Falanga V, Wound healing and its impairment in the diabetic foot, The Lancet, Volume 366, Issue 9498, Pages 1736 - 1743, 12 November 2005
62. Steed DL, Donohoe D, Webster MW, Lindsley L, Effect of extensive debridement and treatment on the healing of diabetic foot ulcers. Diabetic Ulcer Study Group. Journal of the American College of Surgeons [1996, 183(1):61-64
63. Steed DL, the Diabetic Ulcer Study Group, Clinical evaluation of recombinant human platelet – derived growth factor for the treatment of lower extremity diabetic ulcersJournal

of Vascular Surgery, Volume 21, Issue 1, January 1995, Pages 71–81
64. Armstrong DG, La terapia a pressione negativa della ferita e altre nuove terapie per le ulcere del piede diabetico: l'attuale stato dei fatti. Med Clin North Am. 2013 Sep;97(5):899-909
65. Barth R, Campbell IV, Allen S et al. Intensive education improves knowledge, compliace and foot problems in type 2 diabetes. Diabetic Med 8: 111-117; 1991
66. International Working Group on the Diabetic Foot. Documento di Consenso Internazionale piede Diabetico. Terza Edizione Italiana 2010 p. 202-203
67. Martin RL, Conti SF. Plantar Pressare analysis of diabetic rockerbottom deformity in total contact casts. Foot Ankle Int 17: 470-472; 1996
68. Tsung BYS, Zhang M, Mak AFT, Wong MWN. Effectivness of insoles on plantar pressure redistribution. J Rehabil Res Dev 41: 767-774; 2004
69. Lavery LA, Vela SA, Lavery DC, Quebedeaux TL. Reducing dynamic foot pressures in hight-risk diabetic subjects with foot ulcerations. A comparison treatments. Diabetes Care 19: 818-821; 1996

Received: 23 July 2014
Accepted: 13 September 2014
Correspondance:
Sergio Tardio, MD
SSD Intensive treatment of diabetes
and its complications
University Hospital of Parma
E-mail: stardio@ao.pr.it